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Systems Analysis of Arterial Pressure Regulation and Hypertension[1,2]

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In this paper we have presented briefly three different aspects of arterial pressure regulation and of the hypertension problem: (1) the basic principles of arterial pressure control, progressing from simple, individual regulatory mechanisms to complex interactions between these mechanisms; (2) several systems analyses of arterial pressure regulation and of hypertension, also progressing from simple to complex; and (3) animal and human verification of both the logical principles and the systems analyses.

Both the systems analyses and the experiments on which they are based show that different feedback control mechanisms are responsible for acute versus long-term control of arterial pressure. Furthermore, some of the concepts of pressure control based on acute experiments and then extrapolated to the problem of hypertension have proved to be wrong, such as the widely heralded concept that chronic hypertension is "caused by" increased total peripheral resistance. Though, on the surface, this concept has long appeared to be a logical one, the systems analysis approach has made it possible to differentiate between the primary causes of hypertension and dependent variables of the system. The basic causes of chronic hypertension predicted by the analyses are: (1) abnormally low renal output of water and electrolytes (mainly salt) at each arterial pressure level, and (2) excess net intake of water and electrolytes. Other causes of chronic hypertension must operate by affecting one of these two basic effects. Total peripheral resistance is one of the dependent variables of the pressure control system, as is also cardiac output, but is never a primary determinant of the long-term level of arterial pressure.

SYSTEMS ANALYSIS OF ARTERIAL PRESSURE REGULATION AND HYPERTENSION

Arterial pressure is not regulated by a single pressure feedback system, but, instead, by multiple feedbacks. Therefore, an understanding of arterial pressure regulation can hardly be achieved without resort to a reasonably complex systems analysis, either a formal analysis or an informal one within the logic of our minds. The goal of the present paper is to present one such systems analysis and some of the conclusions that have been drawn from its application. The analysis, wherever possible, has been based on animal experimental results, and its predictions have also been compared with the results of animal and human experiments.

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[2] This paper is based on the ALZA lecture given by Arthur C. Guyton before the Annual Meeting of the Biomedical Engineering Society in Baltimore, Maryland, April 7, 1972.

The problem of hypertension is a special case of abnormal arterial pressure regulation. In most instances of hypertension, one is concerned with long-term elevation of the arterial pressure. Therefore, one can readily understand that the arterial pressure regulatory mechanisms that have long-term regulatory capability are the ones that will be most concerned in hypertension. Indeed, one of the most beneficial results of this systems analysis has been to show the fallacy of translating short-term animal experimental results into long-term predictions related to hypertension.

As a starting point for this analysis, let us list some of the more important pressure regulatory mechanisms as follows.

(1) *The baroreceptor reflex pressure regulating mechanism.* One of the most widely understood of the pressure regulating mechanisms is the baroreceptor reflex. An increase in arterial pressure excites stretch receptors in the carotid sinuses and in the walls of the aortic arch and of other large arteries. Signals from these stretch receptors, after passing through the medulla, cause reflex decrease in cardiac activity and reflex dilatation of the peripheral blood vessels, which effects tend to reduce both cardiac output and peripheral resistance. Therefore, the arterial pressure returns toward normal. If the arterial pressure falls below normal, this mechanism operates in reverse.

(2) *The chemoreceptor mechanism for arterial pressure regulation.* When the arterial pressure falls to reasonably low values, usually below 80 mm Hg (Heymans *et al.,* 1958), the blood flow to the carotid and aortic bodies decreases enough that the chemoreceptor cells in these bodies receive less than adequate amounts of oxygen; they also accumulate carbon dioxide that is not carried away by the blood. These changes in dissolved gas concentrations cause the chemosensitive cells to transmit signals to the brain and thence back to the circulatory system, this time having the opposite effects on the circulatory system to those caused by the baroreceptor signals, namely, increased cardiac activity and increased peripheral vasoconstriction. Therefore, a decrease in arterial pressure to low values elicits a chemoreceptor reflex that tends to raise the pressure back toward normal.

(3) *The central nervous system ischemic response.* When the arterial pressure falls below approximately 60 mm Hg, and especially below 40 mm Hg (Sagawa *et al.,* 1961), the vasomotor center in the medulla of the brain becomes directly excited, probably because blood flow through the medulla becomes too little to remove carbon dioxide generated by the brain tissues. Again, very powerful signals are sent by way of the autonomic nerves to the circulatory system to increase cardiac activity and to increase the degree of peripheral vasoconstriction, thereby returning the arterial pressure back toward normal.

(4) *Stress-relaxation of the circulation.* When any effect causes a sudden increase in pressure in a given part of the circulation, the vessels stretch almost immediately because of their elastic characteristics. However, they have an additional characteristic of stress-relaxation which causes them to stretch still more over a period of time because of the elevated pressure (Alexander *et al.,* 1953). Stretching of the vessels reduces the effective degree of filling of the vessels by the blood volume that is available, and, if the small peripheral vessels are involved in

the stress-relaxation phenomenon, this will also reduce the peripheral resistance. Consequently, the pressures everywhere in the circulation will tend to return toward the original value.

(5) *Transfer of fluid through the capillary membranes.* In some conditions in which the arterial pressure becomes elevated, the capillary pressure is elevated simultaneously. If this occurs, fluid filters from the circulation into the interstitial spaces. This reduces the blood volume, which in turn reduces the overall flow of blood through the circulation and thereby returns the arterial pressure back toward normal (Guyton *et al.*, 1950).

(6) *The renin-angiotensin-vasoconstrictor system.* When the arterial pressure falls below normal, the kidneys secrete a substance called *renin* into the circulating blood. The renin, which is an enzyme, then causes angiotensin to be split from *renin substrate* which is one of the plasma proteins. The angiotensin, in turn, causes intense constriction of the peripheral arterioles, thus increasing the total peripheral resistance (Page *et al.*, 1968). The net effect is an increase in arterial pressure back toward normal.

(7) *The renal-body fluid feedback pressure control system.* When the arterial pressure rises above normal, the rate of loss of water and salt in the urine increases rapidly. This causes progressive decrease in extracellular fluid volume, which is followed by decreases in blood volume, filling pressure of the circulation, venous return, and cardiac output. The reduced cardiac output in turn reduces the arterial pressure back toward normal. Conversely, if the arterial pressure falls too low, the output of water and salt from the kidneys becomes less than the normal daily intake of these two substances, in which case reverse effects occur and the arterial pressure rises back toward normal (Guyton *et al.*, 1967).

(8) *Aldosterone control of arterial pressure.* The hormone aldosterone causes the kidneys to retain water and salt. Therefore, an increase in the rate of secretion of aldosterone by the adrenal glands will tend to increase the extracellular fluid volume, blood volume, and other factors listed above until the arterial pressure rises to an elevated value. It is also known that in general, though this is not always true, an increase in arterial pressure tends to reduce the rate of aldosterone secretion, while a decrease in arterial pressure tends to enhance aldosterone secretion (Davis, 1962). Therefore, one can readily see that an aldosterone feedback mechanism can act in parallel with the renal-body fluid mechanism to help control arterial pressure. It also acts in concert with the renin-angiotensin system because angiotensin stimulates the secretion of aldosterone. This is in addition to the vasoconstrictor effect of angiotensin, which also elevates the arterial pressure.

In addition to the above well-characterized control mechanisms, still other arterial pressure control mechanisms play minor, or perhaps in some instances major, roles in the control of arterial pressure. For instance, pressure feedback loops operate through antidiuretic hormone secreted by the hypothalamic-hypophyseal system, through alterations in body electrolyte compositions, possibly through vasodilator hormones, and possibly through yet undiscovered additional factors such as a so-called "third factor" for control of sodium excretion by the kidneys and a so-called "fourth factor" for control of aldosterone secretion by the adrenal glands.

LOOP GAINS AND TIME COURSES OF ACTION FOR THE DIFFERENT PRESSURE CONTROL MECHANISMS

A simple way to look at the different pressure control mechanisms is to determine the feedback gains of their control loops and to determine the time courses of the changing gain values for each of the control mechanisms after a given pressure disturbance occurs. Unfortunately, too little information is available to be very precise about these parameters for any one of the pressure control systems. However, Fig. 1 illustrates a preliminary attempt to give at least approximate values for both the gains and their approximate time courses following a sudden change in arterial pressure for the eight well-characterized pressure control mechanisms (Guyton *et al.*, 1972a). The solid portions of these curves are based on reasonably valid experimental results, while the dashed portions of the curves are still very hypothetical.

Note especially in Fig. 1 that the time scale on the abscissa is approximately logarithmic, beginning with seconds and then proceeding to minutes, hours, and days. Note also that the three nervous pressure control mechanisms begin to act within seconds and reach full development within approximately one minute. Then come several control systems with intermediate reaction times, including the stress-relaxation mechanism, the renin-angiotensin-vasoconstrictor mechanism, and the capillary fluid shift mechanism, all of which begin to act within minutes and reach full development within 20 minutes to several hours. Finally

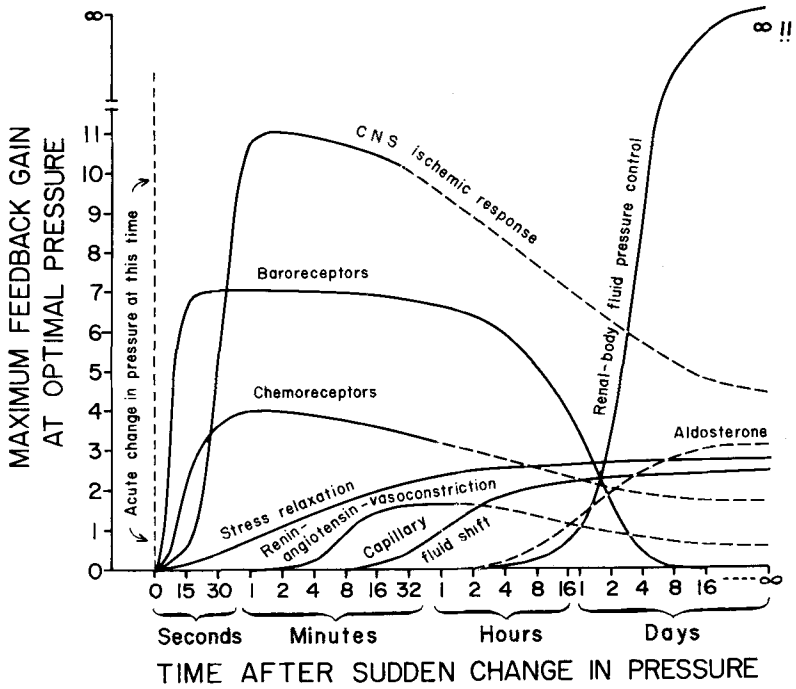

FIG. 1. Feedback gains and their time-courses for eight of the important arterial pressure control mechanisms. (Preprinted from: Guyton *et al.*: *Arterial Pressure Regulation.* W. B. Saunders Co.)

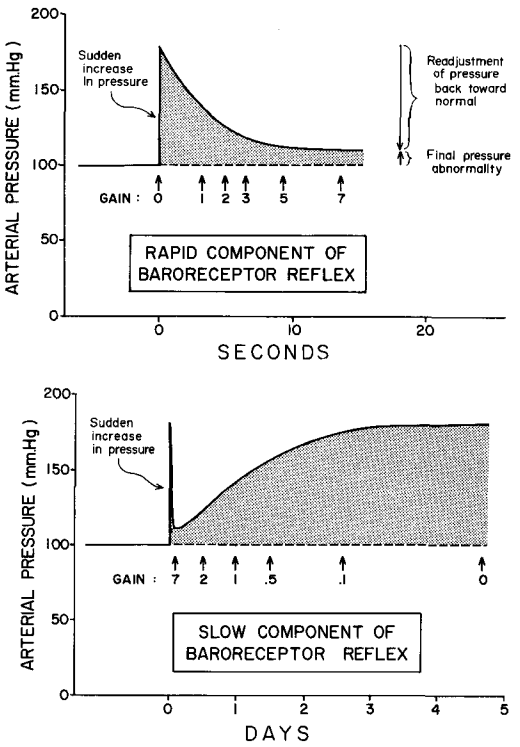

FIG. 2. Time-response of arterial pressure readjustment caused by the baroreceptor system when the arterial pressure is suddenly elevated by some extraneous cause to 80 mm Hg above normal. (A) Response in the first few seconds. (B) Response over a period of days, showing "resetting" (or "adaptation") of the baroreceptors. (Reprinted from: Guyton *et al.* In Genest and Koiw, Eds. *Hypertension,* Springer-Verlag, 1972.)

come the more slowly acting mechanisms, the renal-body fluid mechanism and its associated mechanism of aldosterone control, each of which begins to act very soon after a pressure change occurs, but each of which requires many hours or days to affect arterial pressure greatly because the entire body fluid composition must be shifted considerably before the secondary effects on the arterial pressure become effective.

Therefore, one can see that the overall symphony of systems for regulating arterial pressure is comprised of pressure regulating mechanisms capable of acting extremely rapidly (the nervous mechanisms), at intermediate time intervals, or over extremely long time periods (especially the renal-body fluid mechanism).

Figure 2 illustrates a typical type of experiment that has been used to measure the gain and its time course for one of the more important pressure control mechanisms, the baroreceptor reflex system. The time scale in Fig. 2A is expressed in seconds while that of 2B is in days. At zero time, the arterial pressure is suddenly increased in some way, such as sudden transfusion of blood into the circulation, from the normal value of 100 mm Hg up to approximately 180 mm Hg. The baroreceptor reflex begins to act within seconds; and within 10 to 15 sec the pres-

sure has fallen to a new plateau level of approximately 110 mm Hg. Thus, the initial pressure abnormality is 80 mm Hg, and the pressure abnormality after the baroreceptor reflex system has become completely active is approximately 110 mm Hg. Since gain can be determined by dividing the amount of correction (70 mm Hg at the end of 15 sec) by the final pressure error (10 mm Hg at the end of 15 sec), one finds that the gain of the baroreceptor reflex at 15 seconds is sometimes as great as seven (Dobbs *et al.*, 1971). This is the effect that is observed following sudden infusion of excess blood volume, which raises the pressure in the systemic arterial bed, in the pulmonary arterial bed, and in the heart chambers all simultaneously, thus giving a number of mutually supportive baroreceptor reflexes from several different sources. When the pressure is elevated in the arterial tree alone, the maximum gain is about two (Scher *et al.*, 1962). Note also the time course of the gain, beginning with zero gain at zero seconds after the pressure has been made suddenly abnormal and developing a gain of approximately 1 at 3 sec, approximately 3 at 7 sec, and 7 at 15 sec.

Now observe Fig. 2B which shows that even though a gain of the baroreceptor reflex mechanism is seven within a few seconds after an abnormal pressure change, this gain slowly disappears over a period of several days, a phenomenon called *resetting of the baroreceptors* or *adaptation of the baroreceptors* (Kezdi *et al.*, 1967). Therefore, one can immediately recognize that the baroreceptor system can be of major value for moderating arterial pressure changes when the factor tending to cause a pressure abnormality lasts for seconds, minutes, or hours, but not if the abnormality lasts for longer than a few days. Therefore, we must look to long-acting control systems for control of the day in and day out mean level of arterial pressure.

Figure 3 illustrates another example of function by a pressure feedback control system, this time the renal-body fluid mechanism. Let us assume that greatly excess quantities of water and salt have been infused into an animal or into a person for a long period of time until the arterial pressure has become adjusted to a very high level; then suddenly the infusion of water and salt is stopped. At this point, the renal-body fluid feedback mechanism begins to rid the body of ac-

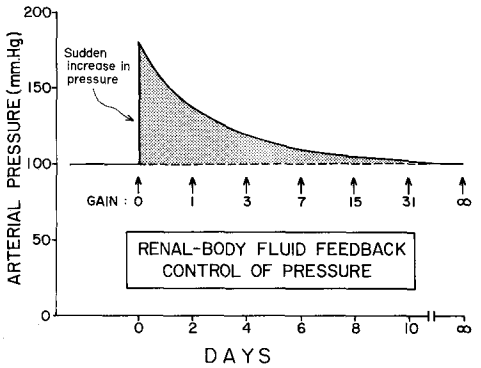

FIG. 3. Time-course of arterial pressure readjustment caused by the renal-body fluid-arterial pressure control system following elevation of the arterial pressure to a high level because of some extraneous factor. (Reprinted from: Guyton *et al.* In Genest and Koiw, Eds. *Hypertension,* Springer-Verlag 1972.)

cumulated excess fluid and thereby to reduce the arterial pressure toward normal (Langston *et al.,* 1963). A major share of this effect occurs in the first few days, but the effect theoretically continues for an infinite period of time, with the pressure approaching the original normal arterial pressure value as a limit at infinite time. When one calculates the gain of this system at different time intervals, it is zero at zero time and then progresses to a gain of perhaps one in one to two days, a gain of five to ten within six days, and, very interestingly, a gain of infinity at infinite time. Indeed, the system reaches a gain that is so great within two to three weeks that it can, for practical purposes, be considered to be infinity after that time. This explains the extremely high gain that is noted both in Fig. 1 and in Fig. 3 for the renal body fluid feedback mechanism for control of arterial pressure. This effect proves to be extremely important in the long-term regulation of arterial pressure and, therefore, will be explained in much greater detail in the course of this paper.

THE BASIC RENAL-BODY FLUID–ARTERIAL PRESSURE FEEDBACK LOOP

Since the renal-body fluid–arterial pressure feedback mechanism can (under some conditions) display infinite gain and since it is also a long-term control system that plays a major role in year after year establishment of the average basal level of arterial pressure, it is appropriate to begin our systems analysis with a consideration of the basic factors that make up this pressure feedback control loop (Guyton *et al.,* 1967). Figure 4 illustrates the eight essential blocks of the loop. These may be described as follows.

(1) Block 1 shows the effect of arterial pressure (AP) on output of extracellular fluid [$dE/dt(o)$] (which is the main constituent of urine) by the kidneys. Note that a decrease in arterial pressure from the normal value of 100 mm Hg down to approximately 60 mm Hg causes complete cessation of urinary output, while an increase in arterial pressure to 200 mm Hg causes a 6 to 8 fold increase above normal in output of both water and salt, thus causing rapid loss of extracellular fluid from the body.

(2) Block 2 shows the summation of the output of extracellular fluid [$dE/dt(o)$] and intake [$dE/dt(i)$]. The output of this block is the rate of change of extracellular fluid volume in the body (dE/dt). The intake of extracellular fluid is defined as the intake by mouth of the water and electrolytes that go to make up the extracellular fluid minus the net loss of these substances through nonrenal routes such as in the feces, through the lungs, through the sweat glands, and so forth.

(3) Block 3 shows the integration with respect to time of the rate of change of extracellular fluid volume, and the output of this block is the extracellular fluid volume itself (E).

(4) Block 4 shows the relationship between extracellular fluid volume and blood volume (BV) in a normal person. This curve has been derived from studies in human beings and has been compared with extrapolated curves of a similar nature determined in dogs (Guyton, unpublished results). The "X" marks the normal state and shows that, in the normal range of function of this curve, an

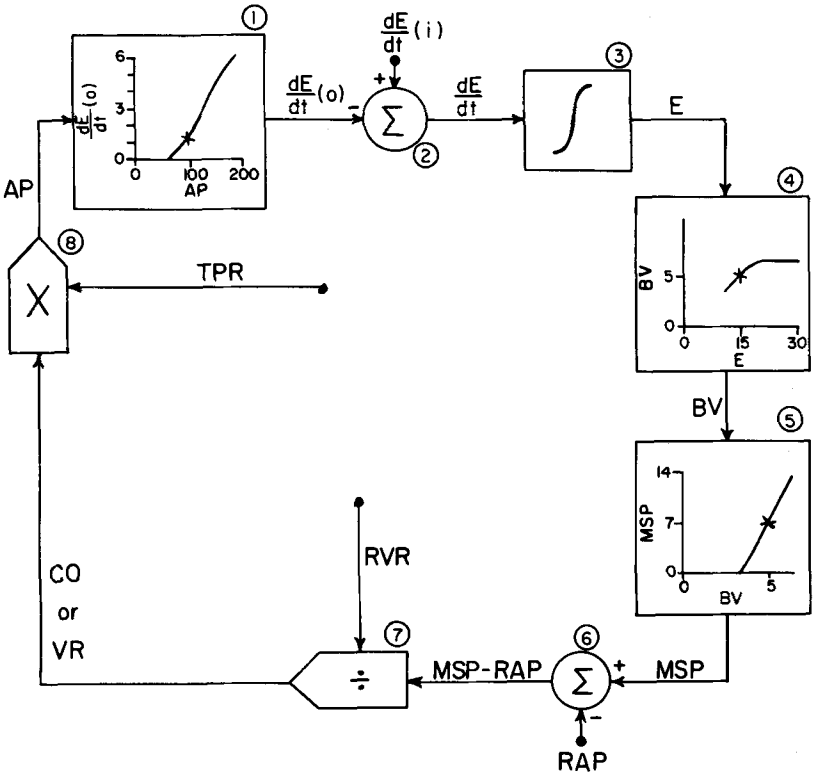

FIG. 4. The basic feedback control loop of the renal-body fluid-arterial pressure control system.

increase in extracellular fluid volume causes approximately one-third as much increase in blood volume. On the other hand, once the extracellular fluid volume rises to the point that edema begins to occur, further increase in extracellular fluid volume has almost zero effect on blood volume.

(5) Block 5 shows the effect of blood volume on the filling pressure of the systemic circulation, expressed as the mean systemic pressure (MSP). This is the theoretical pressure that would exist in the circulatory system if pumping of blood by the heart were suddenly stopped and all pressures throughout the body were brought suddenly to equilibrium. This definition also assumes that the pressure-volume curves of the different segments of the circulation are linear, which is not too far from the truth in the normal ranges of circulatory function for most vascular segments. The mean systemic pressure is important because it is the limiting pressure in the systemic circulation as the pumping capability of the heart decreases. That is, the right atrial pressure rises to approach this value, while the aortic pressure falls to approach this value.

(6) Block 6 subtracts the right atrial pressure (RAP) from the mean systemic pressure. The difference between these two values is important because, both theoretically and experimentally, one can show that the flow of blood from the peripheral circulatory system toward the heart is almost exactly proportional to this difference (Guyton *et al.*, 1955).

(7) Block 7 calculates the venous return (VR) which is inversely proportional to the resistance to venous return (RVR). The term "resistance to venous return" is an algebraically derived term in which the resistances of different parts of the peripheral circulation are weighted in proportion to systemic capacitances proximal to the respective parts (Guyton *et al.*, 1963). One finds that a given amount of added venous resistance affects venous return far more than does the same amount of added resistance further toward the arteries. However, since the greatest resistance changes in the circulation normally occur in the minute vessels of the body, these vessels, too, play a very significant role in determining return of blood to the heart from the peripheral circulation despite the low capacitance of the smaller vessels and of the vascular tree proximal to them. Note that the output of Block 7 is also equal to cardiac output (CO) as well as venous return because, except during a few beats of the heart (that is, in the steady state), the cardiac output must equal the venous return.

(8) Block 8 shows the calculation of arterial pressure by multiplying cardiac output times total peripheral resistance (TPR). Thus, the total loop of the renal-body fluid-arterial pressure control mechanism has now been closed.

The negative feedback properties of the body fluid-pressure control loop. The negative sign of the output of extracellular fluid at Block 2 in the pressure control loop of Fig. 4 gives the entire system the properties of a typical negative feedback control loop. Now, let us see what the effects would be of increasing the arterial pressure to some value above the steady-state level. This will immediately increase the rate of loss of extracellular fluid and, therefore, promote a progressive decrease in extracellular fluid volume. The blood volume will decrease, the mean systemic pressure will decrease, the pressure difference causing venous return will decrease, venous return will decrease, cardiac output will decrease, and arterial pressure will decrease. Furthermore, arterial pressure will continue to decrease until it falls to that pressure level at which the output of extracellular fluid is precisely equal to the intake of extracellular fluid, that is, until the output of Block 2, the rate of change of the extracellular fluid volume (dE/dt), is equal to zero.

Exactly the converse effects will occur if the arterial pressure is reduced below normal, namely, less output of fluid than intake, causing progressive increase in the fluid volumes and in cardiac output until the arterial pressure returns again to its original steady-state value.

THE INFINITE GAIN CHARACTERISTIC OF THE RENAL-BODY FLUID FEEDBACK CONTROL SYSTEM

The integral step in Block 3 in Fig. 4 gives the renal-body fluid feedback control system the characteristics of an integral control system. The input to Block 3, therefore, always tends to approach zero, which is its steady-state value. Therefore, if ever the rate of change in extracellular fluid volume becomes some value besides zero, it tends to reapproach the steady-state value of zero with an ultimate steady-state gain of infinity. However, it will approach this gain only at infinite time, though for practical purposes it approaches an effective gain of infinity within two to three weeks following a disturbance in the system.

Under some conditions, other factors in the control loop of Fig. 4 are also controlled with infinite gain. Let us first consider the output of Block 1, which is the rate of output of extracellular fluid through the kidneys [$dE/dt(o)$]. Since the control system will always return $dE/dt(o)$ to a value exactly equal to $dE/dt(i)$, the output of the kidneys will return always exactly to its steady-state value if the intake of extracellular fluid [$dE/dt(i)$] remains constant, having no final error displacement from the original steady-state level. Therefore, the loop feedback gain for the output of the kidney under the special condition of constant intake of extracellular fluid is also infinity. Thus, in the steady-state condition the single determinant of the output is the intake of extracellular fluid.

Now, we can go back still another step in the analysis to arterial pressure. If the function curve in Block 1 remains precisely constant, and if the intake of extracellular fluid remains constant, the arterial pressure will always return to exactly the same steady-state level. In the normal condition illustrated in Fig. 4, this precise arterial pressure value is 100. If ever it becomes greater than this value or lower than this value, the system variables will automatically change until the arterial pressure returns exactly to this level, provided the above two conditions are met. Therefore, under these two special conditions arterial pressure is also controlled with infinite gain. These two conditions are (1) that the rate of intake of extracellular fluid (mainly water and salt) remains constant, and (2) that the renal function curve depicting output of extracellular fluid with respect to arterial pressure remains exactly constant.

One can go still further backwards in the diagram to show that cardiac output and venous return are controlled with infinite gain if the two conditions for infinite gain control of arterial pressure are satisfied and if the total peripheral resistance remains constant.

In other words one can work backwards from the always infinite gain point of the control system at the input of Block 3 and can establish the conditions that are required for infinite gain in the control of all the respective variables in the total system. Since the extracellular fluid volume is the variable most remotely displaced in the backwards direction from Block 3, it follows that this value has the greatest number of factors which must be established absolutely before it will be controlled with a gain of infinity.

THE TWO DETERMINANTS OF THE LONG-TERM ARTERIAL PRESSURE LEVEL

In the above discussions of infinite gain of arterial pressure by the body fluid system, it was pointed out that there are two conditions required for this system to control arterial pressure with infinite gain, namely, constant intake of extracellular fluid and constancy of the renal function curve as shown in Block 1. Therefore, it is also obvious that changing either one of these two factors will change arterial pressure. Thus, the two primary determinants of the long-term level of arterial pressure can be identified as (1) the net rate of intake of extracellular fluid (in the form of water and electrolytes) and (2) the renal function curve itself. In addition any secondary factors that can change either of these two primary determinants are secondary determinants of the long-term level of arterial pressure.

The mechanism by which the two primary determinants control the long-term level of arterial pressure is illustrated graphically in Fig. 5. The curve labeled "Normal" represents the approximate renal function curve for the normal human being. This curve is steeper than the curve illustrated in Block 1 of Fig. 4 because additional factors not shown in the primary feedback loop of Fig. 4 have been considered. For instance, in Fig. 4 the only way in which a rising arterial pressure can increase the output of the kidney is through the mechanical effect of the rising arterial pressure itself. This is the result one sees when the effect of arterial pressure on renal output is measured in the isolated kidney. However, in the normal human being, an increase in arterial pressure increases the output of urine in several ways besides the direct mechanical effect of the rising pressure, especially by reflex effects acting through the nervous system and by hormonal effects acting through the ADH and aldosterone systems. Though data are very scant for the precise shape of this composite curve for the human being, nevertheless, there are enough data to show that the curve is an extremely steep one in the normal arterial pressure range when the person's kidneys are also normal (Guyton *et al.*, 1972b).

The curve labeled "Normal intake" in Fig. 5 represents the average normal net intake of extracellular fluid in the form of water and salt by the normal human being, approximately 1 ml per min. Net intake in defined as intake by mouth minus losses in other ways besides through the kidneys.

Now, note that the normal renal function curve and the normal intake curve equate with each other at point A. This is the only point at which steady-state conditions can possibly exist in the renal-body fluid-arterial pressure control system. If the arterial pressure rises above this pressure level, the output becomes greater than the intake and the person will become progressively dehydrated until the arterial pressure falls back to normal. Conversely, if the arterial pressure falls below normal, the intake becomes greater than the output until the fluid volumes

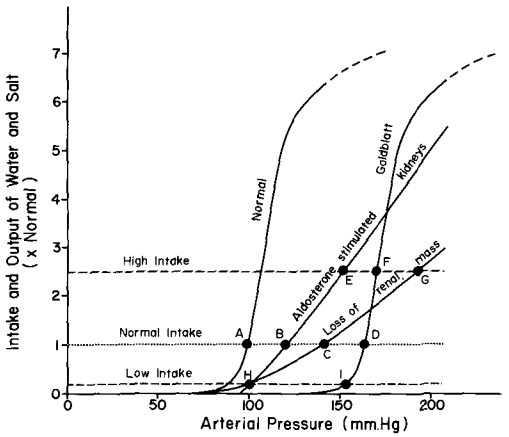

FIG. 5. Equating of renal function curves and fluid intake curves to determine the long-range level of arterial pressure control. Note that the normal renal function curve and the normal intake curve equate at a long-term arterial pressure level of 100 mm Hg. The other curves are explained in the text. (Reprinted from: Guyton *et al. Bulletin of the New York Academy of Medicine,* 1969, **45,** 811.)

increase enough to force a secondary increase in arterial pressure to that level that will bring about equilibrium once again between intake and output.

Thus, the two determinants of arterial pressure are the respective curves in the graph of Fig. 5 which represent net intake of fluid and the effect of arterial pressure on renal output of fluid.

Effect of changing the determinants of arterial pressure. Figure 5 also shows three abnormal renal function curves and two abnormal intake curves, low intake and high intake. Using these curves one can tell readily the effect on arterial pressure level caused by changing from normal either one of the two determinants of long-term arterial pressure. The three abnormal renal function curves represent the approximate curves caused by (1) excess aldosterone secretion, (2) application of Goldblatt clamps to both renal arteries, and (3) loss of renal mass (Guyton *et al.,* 1969a). If one assumes that the intake of water and salt is normal but that there is excess secretion of aldosterone, the arterial pressure will rise from point A to point B. It will rise to point C when there is very significant loss of renal mass, and it will rise to point D when Goldblatt clamps are applied to the renal arteries.

If the level of intake of water and salt is changed, the arterial pressure will be changed in other ways as follows: When the renal function curve is normal, increasing the intake of water and salt has, within wide limits, little effect on the arterial pressure which, indeed, is a well-known fact. Also, in the case of Goldblatt kidneys, changing the intake of water and salt within wide limits (points D, F, and I) also has little effect on the arterial pressure. On the other hand, changing the intake of water and salt has marked effects on arterial pressure in either the condition of excess aldosterone secretion (points B, E, and H) or the condition of greatly decreased renal mass (points C, G, and H). Thus, with a very low intake of water and salt, the arterial pressure can be returned to normal in both of these conditions (point H), while at high intake of water and salt, the arterial pressure is likely to rise to extreme levels in both of these conditions (points E and G). All of these effects are well known in the hypertension literature.

Therefore, without going deeply into the systems analysis of arterial pressure regulation, one can already begin to understand the types of factors that can cause long-term changes in arterial pressure and, to a slight extent, even the mechanisms by which their effects are brought about.

EXPERIMENTAL STUDIES TO VERIFY THE PRINCIPLE OF TWO DETERMINANTS FOR LONG-TERM REGULATION OF ARTERIAL PRESSURE

Figure 6 illustrates average results from a simple experiment in which both the renal function curve was altered and the intake of water and salt was altered in four separate dogs (Langston *et al.,* 1963). After ten days of control studies, the two poles of the left kidney were resected, leaving approximately 60 per cent of the kidney intact. Several weeks later, after healing had occurred in this kidney, the entire second kidney was removed. Therefore, the remaining renal mass was now only 30 per cent of normal. Note that the average arterial pressure increased approximately 7 mm Hg. Removal of this amount of kidney mass was equivalent to reducing the slope of the normal renal function curve in Fig. 5 to approximately

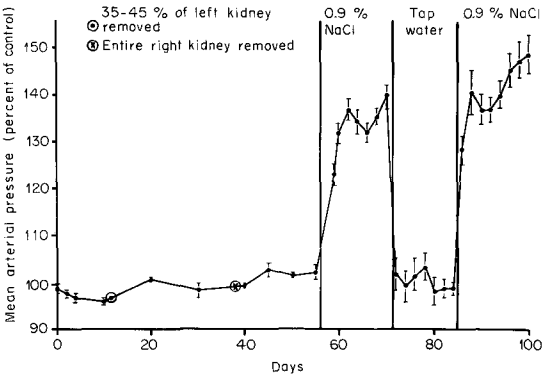

FIG. 6. Hypertension in four dogs, caused by (A) removal of 70% of the renal mass and (B) substitution of the normal drinking water by isotonic saline solution. (Reprinted from: Langston *et al. Circulation Research,* 1963, **12,** 508.)

one-third normal. Such a change would affect the equilibrium point between the renal function curve and the normal intake curve only slightly. Therefore, the average increase in arterial pressure of 7 mm Hg was almost exactly what one would have expected.

At the 55 day mark in the experiment, the dogs with only 30 per cent renal mass were subjected to marked increase in intake of water and salt. This was achieved by requiring the animals to drink isotonic saline solution instead of normal drinking water. Because the saline would not quench the thirst of the animals, they drank an average of three to four times as much of this fluid as they drank of normal water. Note in the figure that the arterial pressure rose rapidly and dramatically. Two weeks later, changing of the drinking solution back to tap water caused the arterial pressure to fall within 24 to 48 hours back to its normal level. Then, two more weeks later, reinstitution of saline drinking caused an even more rapid and more dramatic increase in arterial pressure, the more dramatic effects this time being caused by obviously increased willingness of the animals to drink the salt solution. This increased intake of water and salt was equivalent to increasing the level of the intake curve in Fig. 5 to a level about three to four times normal. In an animal with depressed kidney function, and, therefore, with a depressed slope to its renal function curve, one would expect this increase in salt and water intake to increase the arterial pressure dramatically. Yet, in a normal animal, a similar increase in water and salt intake would be expected to cause relatively little increase in arterial pressure, which was the effect observed (approximately a 10 mm Hg rise in pressure) when normal control dogs were required to drink isotonic saline solution instead of normal drinking water (Langston *et al.,* 1963).

Transient changes in circulatory factors in salt and water loading hypertension. The same experiment as that illustrated in Fig. 6 was performed in additional dogs in which the intake of water and salt was very precisely controlled by infusing isotonic saline intravenously rather than requiring the animals to drink the solution (Coleman *et al.,* 1969). The curves in the left panel in Fig. 7 illustrate the average results from six dogs, showing first a control period of one week run several weeks

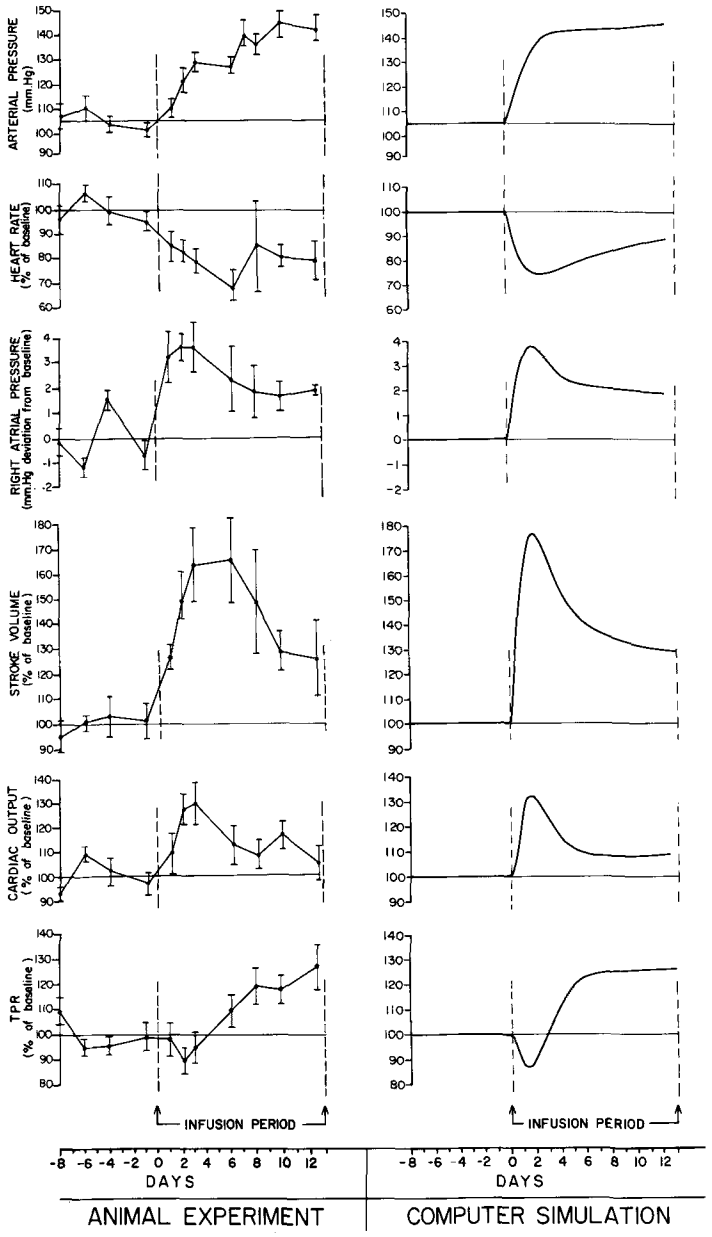

FIG. 7. Left panel: transient changes in different parameters of circulatory function in 6 dogs which had had 70% of the renal mass removed previously and which were infused (between the lines) with isotonic saline at a rate of 2 to 3 liters per day. Right panel: simulated effects of the same experiment using the systems analysis of Fig. 8. (Modified from: Coleman *et al. Circulation Research,* 1969, **25,** 152.)

after 70 per cent of the renal mass had been removed. Then saline was infused at a rate of two to three liters a day for a period of 13 days. The curves show the following respective changes: (1) progressive increase in arterial pressure, reaching a plateau in approximately a week; (2) decrease in heart rate [subsequently shown to be caused by baroreceptor feedback depression of heart rate (Cowley, unpublished observations)]; (3) increase in right atrial pressure at the onset of saline infusion but return of this pressure most of the way toward normal near the end of the 13 day infusion; (4) a drastic increase in stroke volume output at the onset of the hypertension (presumably caused by the Frank-Starling effect of the increased right atrial pressure); (5) increase in cardiac output during the early stages of the infusion but return of cardiac output almost to normal by the end of the infusion; (6) and, finally, an initial decrease in total peripheral resistance but followed by slow increase in total peripheral resistance by the end of the infusion.

These results are in general those which one would expect from the fluid volume concept of arterial pressure regulation. However, many details of the results still cannot be explained by the very simple analysis of Fig. 4. For instance, this analysis predicts that the right atrial pressure, stroke volume output, and cardiac output would all have to rise to high values and remain there to cause chronic hypertension. Also, this simple analysis says nothing about changes in total peripheral resistance and heart rate. Therefore, other important events undoubtedly occur in the animal experiment besides the simple readjustments of fluid volume and other factors illustrated by the simple analysis.

A SYSTEMS ANALYSIS OF INTERMEDIATE COMPLEXITY FOR BLOOD PRESSURE CONTROL

In an attempt to explain some of the details of the transients illustrated by the experimental curves shown in the left panel of Fig. 7, other factors were added to the simple systems analysis of Fig. 4, and a resulting systems analysis of intermediate complexity for regulation of arterial pressure was derived, illustrated in Fig. 8. This analysis still contains the same basic fluid feedback loop of Fig. 5, which is represented once again by Blocks 1–8. The new factors that have been added to this analysis include the following:

(1) *The effect of autoregulation.* When more blood flows through almost any tissue of the body than is required by that tissue for its specific function, the local resistance to blood flow increases progressively until the blood flow returns most of the way back toward normal. This mechanism is usually called "autoregulation" by most researchers in the field of hypertension (Ledingham *et al.*, 1964). This phenomenon of autoregulation is computed in Blocks 9–12 in Fig. 8.

Part of the autoregulation reaction occurs within less than a minute, developing a feedback gain of as much as three to four in some tissues, such as the kidneys, even in this short span of time (Selkurt *et al.*, 1951). However, in most parts of the body a much longer period of time is required. For the total systemic circulation, the autoregulatory gain reaches a value of 1 in approximately 7 min and a value of 3 in approximately 30 min (Granger *et al.*, 1969). That is, an increase in flow through the entire body caused by increased cardiac output will cause enough

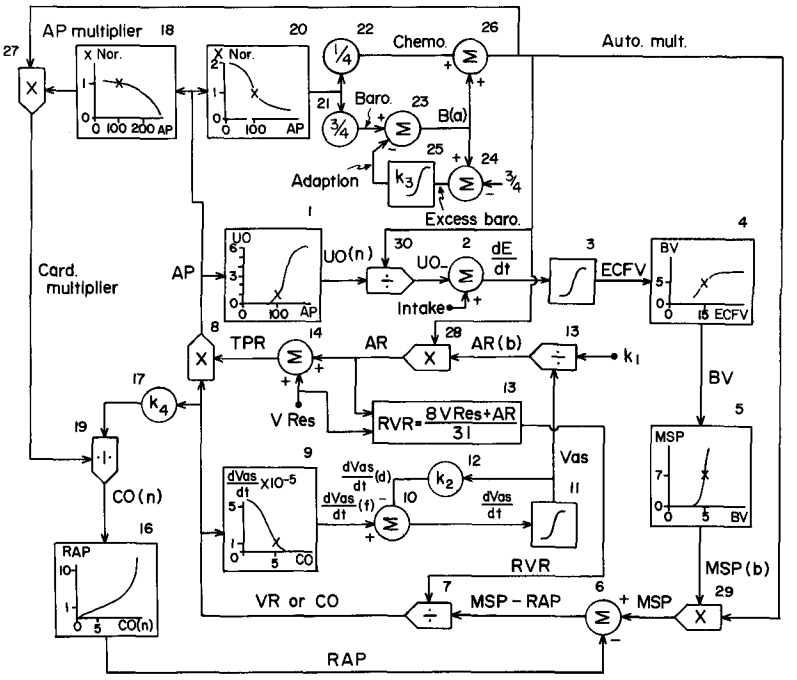

FIG. 8. A systems analysis of intermediate complexity for analyzing arterial pressure control in salt loading hypertension. (Modified from: Guyton *et al.* In Reeve and Guyton, Eds. *Physical Bases of Circulatory Transport,* W. B. Saunders Co., 1967.)

increase in local resistance in approximately one-half hour to return the total flow about three-quarters of the way back toward normal if the arterial pressure does not change. Yet, here again, one sees from results in the left panel of Fig. 7 that the cardiac output required several days to return almost to normal rather than 30 min. Therefore, there must be other factors that are delaying this response. One of these will be described in the following section.

(2) *Neural feedback control of arterial pressure.* Blocks 19–30 of Fig. 8 show the effects of neural control of arterial pressure, depicting very elementarily the reflex effects of the baroreceptor and chemoreceptor systems. Blocks 23–25 compute baroreceptor resetting or adaptation. The output of Block 26 is called the *autonomic multiplier* and represents the combined effects of the two reflex feedbacks on mean systemic pressure (Block 29), arterial resistance (Block 28), renal output (Block 30), and cardiac pumping capability (Blocks 19 and 27). When the arterial pressure begins to rise during the onset of hypertension, it immediately activates these reflexes, causing a decrease in the autonomic multiplier. As a result, the total peripheral resistance decreases (as was illustrated in the experimental results in Fig. 7) and the heart rate decreases. Also, the tendency of the autoregulatory phenomenon to return the cardiac output back toward normal is nullified by the peripheral vasodilatation induced by the reflexes. Recent experiments by Cowley *et al.* in which the baro- and chemoreceptor systems were denervated showed that the arterial pressure rises to its full plateau level in approximately 8 hours instead of the one week required in the experiments illus-

trated in Fig. 7 (Cowley *et al.*, unpublished observations). This substantiates the belief that the nervous reflexes play an exceedingly important role in slowing the rise of arterial pressure during the onset of almost any type of hypertension. It also explains the tremendous decrease in heart rate that is often seen during the onset of hypertension – sometimes to heart rate levels as low as 50 to 60 per cent of normal (Coleman *et al.*, 1969; Crawford *et al.*, 1967).

(3) *Function of the heart in the control of arterial pressure.* In the simple systems analysis of Fig. 4 the right atrial pressure was assumed to remain at a constant level. However, when the load on the heart changes, either in the form of increased volume to be pumped or increased pressure against which the heart must pump, the right atrial pressure will likely also change. Block 16 shows the basic function curve of the heart, illustrating the change in right atrial pressure during increasing volume load on the heart, while Blocks 18, 19, and 27 show the effect of pressure load on the heart. From a quantitative point of view, however, the heart has so much extra pumping capability that it plays only a very minor role in arterial pressure regulation except when the heart is weakened so much that it is in what is known clinically as "cardiac failure." In the analysis of Fig. 8, the heart can be made to simulate the failing condition by increasing constant k_4 in Block 17.

SIMULATION OF SALT LOADING HYPERTENSION USING THE SYSTEMS ANALYSIS OF FIG. 8

The salt loading experiment of the left panel of Fig. 7 was simulated using the systems analysis of Fig. 8, and the results are illustrated in the right panel of Fig. 7. The results from the computer analysis now fit reasonably well the results found in the actual animal experiments, illustrating progressive rise in arterial pressure; transient decrease in heart rate; increase in right atrial pressure which is transiently much greater at first; tremendous increase in stroke volume output which is transiently very great at first and which returns most of the way toward normal by the end of the experiment; transient increase in cardiac output which is also far greater at the beginning of the experiment and which also returns almost to normal by the end of the experiment; and, finally, transient decrease in total peripheral resistance at the beginning of the experiment followed a few days later by a rise in total peripheral resistance which occurs in consequence of resetting of the baroreceptors and development of the autoregulation phenomenon.

Though the simulation results in the right half of Fig. 7 show exactly the same directional changes as observed in the actual animal experiments (Coleman *et al.*, 1969), and though they give essentially correct quantitative values, the time-courses of the different variable changes are still somewhat different from those displayed in the animal experiments. Therefore, it is clear that even the intermediate analysis of Fig. 8 is not sufficient to explain the detailed changes of the experiments. Furthermore, this analysis is not adequate to explain details of other types of circulatory experiments besides those of salt loading hypertension. Therefore, still a much more complex analysis of arterial pressure regulation has been developed.

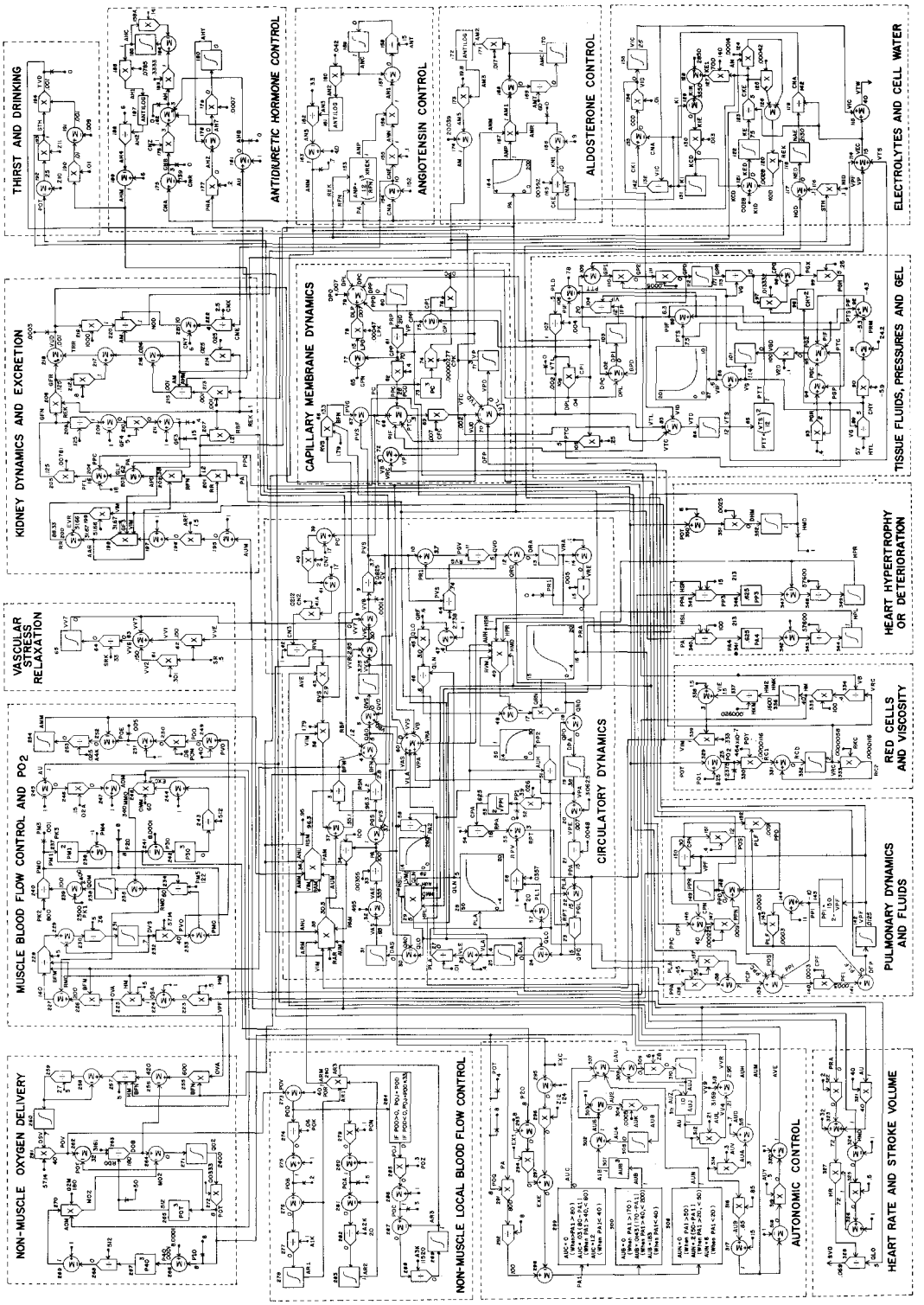

FIG. 9. Systems analysis diagram for regulation of the circulation. (Reprinted in part from Guyton *et al., Annual Review of Physiology*, 1972, **34,** 13. See original reference for definitions of units and symbols.)

A COMPLEX ANALYSIS OF ARTERIAL PRESSURE REGULATION

Figure 9 illustrates still further development of the systems analysis for arterial pressure regulation (Guyton *et al.*, 1972c). This analysis now becomes complex enough that it can be used for studying the regulation of many other aspects of circulatory function besides simply arterial pressure regulation. Though it will not be possible to explain this analysis in detail, its individual parts are evident from the diagram itself, including such factors as circulatory dynamics, capillary membrane dynamics, autonomic control, local control of blood flow, kidney dynamics and excretion, hormonal control of the circulation, interstitial fluid dynamics, and so forth. Some of the major differences between this systems analysis and that of Fig. 8 are the following.

(1) In this analysis, the mean systemic pressure principle has not been used. Instead, its mathematical equivalents of pressure–volume relationships for individual segments of the circulation have been employed, such as for the heart chambers, the arteries, and the veins.

(2) The dynamics of fluid exchange through the capillary membrane and the dynamics of fluids in the tissue spaces are included.

(3) Delivery of oxygen to the tissues is analyzed, and the effect of tissue Po_2's on local blood flows is considered.

(4) Control of the circulation by the three hormones aldosterone, angiotensin, and antidiuretic hormone is also considered.

(5) Dynamics of the pulmonary system is separated from dynamics of the systemic circulation.

(6) Stress-relaxation is added to the circulatory system.

(7) Control of body fluid intake by the thirst mechanism is included.

(8) Control of red cell mass and its effect on blood volume has been added.

(9) Effect of cardiac nutrition and cardiac load on heart hypertrophy or deterioration has been considered.

The overall analysis has been used to simulate many different experimental and clinical conditions, including salt loading hypertension, Goldblatt hypertension, congestive heart failure caused by total heart damage, left heart failure, right heart failure, pulsus alternans, vasomotor waves of the circulation, nephrosis, effects of fluid infusion, of polycythemia, of anemia, dehydration, exercise, sympathectomy, excess sympathetic activity, and others. In general, the predictions from the simulations are surprisingly similar to the effects that one observes in actual experimental or clinical conditions, as has been shown by previously published simulations using this systems analysis (Guyton *et al.*, 1972c; Guyton *et al.*, in press) and as illustrated in Figs. 10, 12, and 13 of this paper.

Simulation of salt loading hypertension using the complex systems analysis. Figure 10 illustrates simulation of salt loading hypertension of the same experimental type as that illustrated in Figs. 6 and 7. The control values for the various variables are shown at the beginning of the respective curves. At the end of one day, the renal mass was suddenly reduced to 0.3 normal and the intake of salt was increased to 5 times normal. Thus, the net salt load that each unit mass of kidney

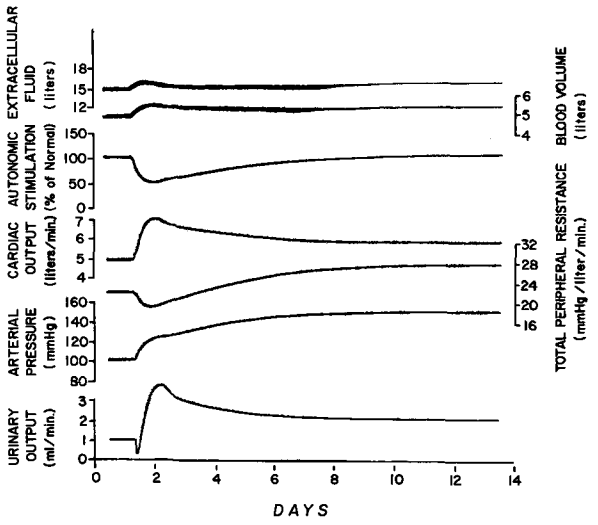

FIG. 10. Simulation of salt loading hypertension, using the complex analysis of Fig. 9. (Reprinted from: Guyton *et al. Annual Review of Physiology,* 1972, **34,** 13.)

had to excrete was increased approximately 16 fold. The simulated results were retention of moderate amounts of salt in the body, activation of the thirst mechanism, increase in water intake, and a greatly increased urinary output (shown by the lowermost curve) despite the reduction in renal mass. The extracellular fluid volume increased, blood volume increased, cardiac output increased, and arterial pressure began to increase. However, the rise in arterial pressure elicited baroreceptor reflexes which reduced (1) total peripheral resistance and (2) degree of autonomic stimulation of the circulation as evidenced by decreased heart rate. Later in the course of events, as the baroreceptors became reset to their higher pressure level, and as the phenomenon of autoregulation developed, the total peripheral resistance rose to a high value while the cardiac output returned almost to normal.

Thus, the results of Fig. 10 simulate almost exactly the experimental results of Fig. 7. Therefore, addition of more controls to the systems analysis makes it possible to simulate the salt and water loading hypertension experiment reasonably accurately.

Salt and water loading hypertension in human beings. Figure 11 is an experiment performed in a human being (Coleman *et al.*, 1970) to show that the salt and water loading hypertension depicted experimentally in Fig. 7 and as simulated using the complex systems analysis in Fig. 9 is not merely an esoteric result peculiar to animals and to the systems analysis. The human being of this experiment had had both kidneys removed and was being maintained on chronic artificial kidney dialysis. The initial value for each curve in the figure was a control value that had been stable for several weeks. At this point the patient was purposely made to gain excess quantity of extracellular fluid by failing to remove the natural increase in fluid at the times of dialysis; the increase in weight depicts the increase in fluid. The effects were concurrent increases in both cardiac output and arterial pressure. However, the total peripheral resistance fell at first

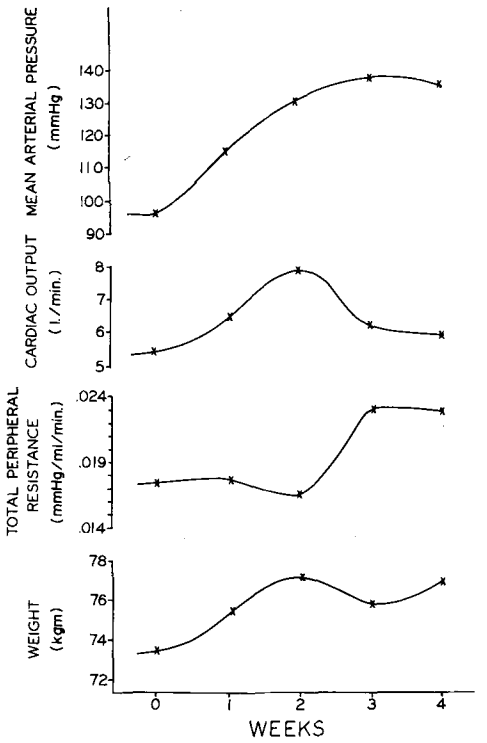

FIG. 11. Changes in several variables of circulatory function in a human being in whom the two kidneys had been removed, who was being maintained by artificial kidney dialysis, and in whom the body weight was allowed to increase several pounds because of accumulation of increased extracellular fluid. (Reprinted from: Coleman *et al. Circulation,* 1970, **42,** 509.)

rather than increasing. Indeed, about 90% of the increase in arterial pressure had already occurred before the total peripheral resistance began to rise at all. Approximately two weeks after the onset of increased body fluids the total peripheral resistance did begin to increase while the cardiac output returned toward normal but the arterial pressure remained elevated.

One can see from these results that almost identically the same effects occur in the human being during the onset of salt and water loading hypertension as in animals and as predicted by the systems analysis.

ROLE OF TOTAL PERIPHERAL RESISTANCE IN THE CONTROL OF ARTERIAL PRESSURE: LESSONS TO BE LEARNED FROM ARTERIOVENOUS FISTULAS

Returning again to the simple systems analysis of Fig. 4 and to the discussion relating to it, it will be recalled that the two determinants of the long-term level of arterial pressure are (1) the intake of extracellular fluid and (2) the renal function curve. Total peripheral resistance, though long believed to be one of the major

factors controlling arterial pressure in both acute and chronic states, falls into the category of a dependent variable. Under many conditions an increase in total peripheral resistance does indeed occur simultaneously with increases in arterial pressure, but this is not at all a necessary relationship, which is easily understood from the systems analysis of Fig. 4 and which becomes even clearer with deeper study of the systems analyses of Figs. 8 and 9.

One can discern two basic reasons from the complex systems analysis of Fig. 9 for the usual high degree of correlation between total peripheral resistance and arterial pressure. The first of these is that many factors which increase total peripheral resistance also shift the renal function curve toward much higher pressure levels. Some examples of these factors are: (1) sympathetic reflexes, that constrict peripheral vessels and simultaneously constrict renal vessels, (2) vasoconstrictor drugs, which affect both peripheral vessels and the renal function curve simultaneously, (3) application of Goldblatt clamps to the kidneys, which shifts the renal function curve toward higher arterial pressures and at the same time causes secretion of the vasoconstrictor substance angiotensin that, at least in the acute phase of Goldblatt hypertension, elicits marked increase in total peripheral resistance.

The second reason for the high degree of correlation between total peripheral resistance and arterial pressure is that every time cardiac output increases, this generally elicits the autoregulatory response in the local vasculature of the tissues, and this increases the total peripheral resistance. In turn, the increase in total peripheral resistance reduces the cardiac output back toward normal. Thus, whenever the arterial pressure is increased as a result of increased cardiac output, the autoregulatory phenomenon automatically substitutes increased total peripheral resistance at least partially, and often almost completely, for the increase in cardiac output. Therefore, one gains the impression that arterial pressure is almost invariably elevated as a result of increased total peripheral resistance. Yet, both the experiments and the systems analyses illustrated in this paper have shown that the initial effect in salt and water loading hypertension is increased cardiac output and that the increase in total peripheral resistance occurs *after* the increase in pressure. However, an even more accurate way to express this is to state that both cardiac output and total peripheral resistance are dependent variables in long-term control of arterial pressure and that either one of them can be utilized by the overall control mechanism, often interchangeably, to raise or lower the arterial pressure. Therefore, it is usually academic to argue whether or not the different types of hypertension are "caused" by elevated total peripheral resistance or elevated cardiac output, even though the literature is full of this type of argument.

Failure of correlation between arterial pressure and total peripheral resistance when arteriovenous fistulas are opened and closed. Figure 12 illustrates simulation of opening and closing an A-V fistula, using the complex systems analysis of Fig. 9 (Guyton *et al.*, in press). Even with a flow through the fistula equal to the normal level of cardiac output, it is predicted that the cardiac output will rise almost enough within seconds after opening the fistula to compensate for the extra flow through the fistula and that the arterial pressure will fall only slightly, except for the first 5–15 sec when the nervous reflexes have not had time to act fully. At

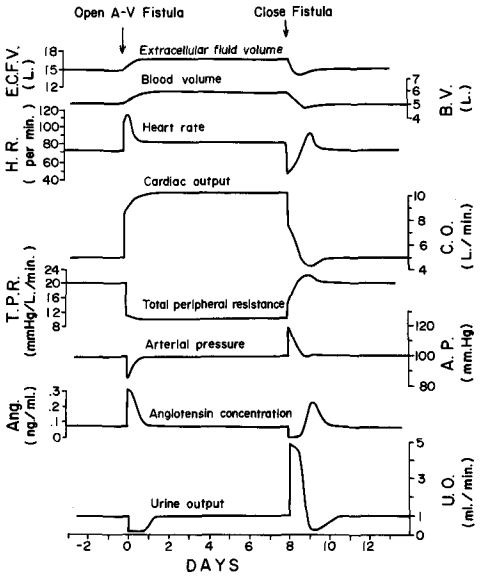

FIG. 12. Simulation of changes in circulatory function following opening of a massive arteriovenous fistula and closure of the same fistula one week later.

the end of approximately a day, the cardiac output is then great enough to compensate completely for the fistula flow, and arterial pressure by then will have returned precisely to the normal level. Yet, the total peripheral resistance is vastly decreased to only 50 per cent of normal. The analysis also shows that among the major factors in these compensatory moves are increases in extracellular fluid volume and blood volume but that only small changes in both of these are sufficient to perform their duties. After remaining open for a week, the fistula is closed, and all the factors return to normal within several days, including loss of the extra fluid that has been gained in the meantime.

The results illustrated in Fig. 11 are almost precisely the same as those found in animal experiments by Holman (1937) and found by Warren *et al.* (1951) in human beings in whom A-V fistulas were closed, including the initial changes in arterial pressure but return of the pressure to normal soon thereafter, the changes in fluid volumes, and the changes in heart rate at the onset and offset of fistula flow.

Since the phenomenon of opening and closing an A-V fistula represents a way in which total peripheral resistance can be changed without other complicating factors, one can see that total peripheral resistance *per se* is not a determinant of the long-range level of arterial pressure. Indeed, it is nothing more than one of the dependent variables that is usually utilized in pressure control.

Another clinical condition that further substantiates the lack of necessary correlation between total peripheral resistance and arterial pressure is the effect of removing all four limbs from a human being. Such persons have total peripheral resistances approximately 60 per cent above normal. Yet, their arterial pressures are known to be the same as those of normal persons.

SIMULATION OF GOLDBLATT HYPERTENSION

Figure 13 illustrates simulation of Goldblatt hypertension, using the complex analysis of Fig. 9 (Guyton *et al.*, in press). There are considerable differences in the results of this analysis from those of salt and water loading hypertension. Note especially the biphasic cardiac output, which can explain why Olmstead and Page (1965) found the cardiac output to be decreased at the onset of Goldblatt hypertension while Ledingham (1964) found it to be increased. Results from Bianchi's laboratory (Bianchi *et al.*, 1970) in Milan, Italy, and results from our own laboratory have shown both effects: decreased cardiac output sometimes during development of hypertension and increased cardiac output at other times.

Note also the great increase in angiotensin at the onset of the hypertension and, yet, return of the angiotensin level essentially to normal a week or so later. This, too, is a very well-known effect of Goldblatt hypertension.

Also the increase in the extracellular fluid volume illustrated in this analysis has been shown by Douglas (1962), Liard (1970), and Bianchi (1970).

The decrease in heart rate shown by this analysis is another known effect during the onset of Goldblatt hypertension (Crawford *et al.*, 1967).

The biphasic effect on total peripheral resistance shown in Fig. 13 was demonstrated in Bianchi's experimental production of Goldblatt hypertension (Bianchi *et al.*, 1970) in which he increased the renal arterial resistance using a clamp that could be closed from the exterior of the body without operative intervention at the time of closure. Indeed, Bianchi measured most of the parameters illustrated in

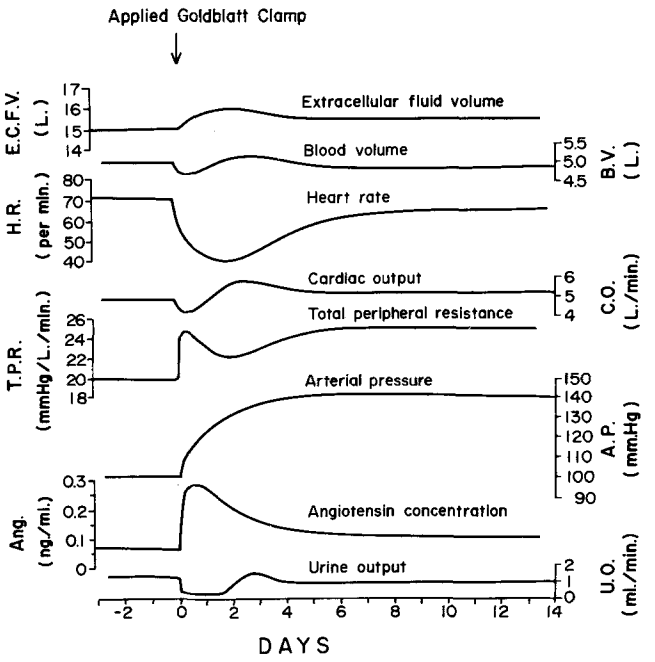

FIG. 13. Simulation of changes in circulatory function during the onset of Goldblatt hypertension.

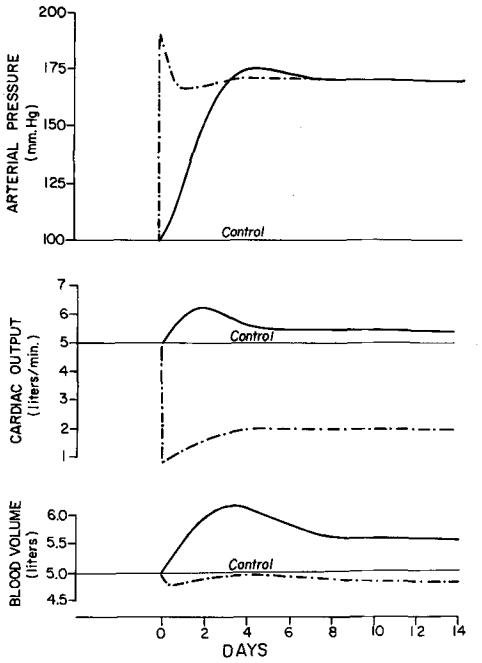

FIG. 14. Simulation of the rise in arterial pressure in renal hypertension under two conditions: (a) solid curves—the renal abnormality causes only salt and water retention; (b) dashed curves—the renal abnormality causes salt and water retention plus activation of the renin-angiotensin-vasoconstrictor system. (Reprinted from: Guyton and Coleman. *Circulation Research* (Supp. I), 1969, **24,** 1.)

Fig. 13 and found that their quantitative values and their time-courses changed almost exactly as illustrated in this figure.

Role of peripheral vasoconstriction in the causation of renal hypertension. Most investigators in the field of renal hypertension, and especially in the field of Goldblatt hypertension, have postulated the "cause" of renal hypertension to be peripheral vasoconstriction or other circulatory effects caused by renin or some other substance released by the kidney (Page *et al.,* 1968). In many, if not most types of renal hypertension, the renal abnormality affects arterial pressure regulation in two different ways: First, it reduces the renal output of water and salt; second, it causes secretion of renin, leading thence to the formation of angiotensin. The angiotensin causes peripheral vasoconstriction and also increased secretion of aldosterone followed by the effect of aldosterone on the kidneys to cause still more salt and water retention. It is essential to answer the question: which of these two effects is the important one in causing hypertension? Though most investigators have come to the conclusion that it is the renin-angiotensin effect that is important, the systems analysis indicates that it is the fluid retention effect (Guyton and Coleman, 1969b). The analytical results which indicate this are illustrated in Fig. 14.

Figure 14 shows simulation of renal hypertension under two different conditions. The first condition assumes that the kidney abnormality promotes only re-

tention of water and salt and does not elicit a renin-angiotensin effect at all. The results in this condition are displayed by the solid curves. Note that the arterial pressure is slow to rise and that the rise is associated with transient initial increases in cardiac output and blood volume, both of which return near to normal in the steady-state period.

The second simulation condition is that the renal abnormality promotes both (1) decreased salt and water excretion by the kidneys at any given arterial pressure and (2) activation of the renin-angiotensin-vasoconstrictor response. It is also assumed that the renal abnormality, once it begins, promotes angiotensin formation at a constant rate thereafter and, therefore, elicits a continuous vasoconstrictor effect on all nonrenal peripheral blood vessels but not on the intrarenal vessels. Since the time-constant for activation of the renin-angiotensin system is very short (about eight minutes), the arterial pressure rises within minutes, but the cardiac output falls as a result of the increased peripheral resistance. Note especially, though, that the arterial pressure eventually becomes exactly the same value as that caused by the salt and water retention alone and that the steady-state differences in the results between the two conditions of simulation are (1) reduced cardiac output and (2) reduced blood volume when the angiotensin-vasoconstrictor mechanism is functioning.

Thus, the simulated results of Fig. 14 indicate that the cause of the hypertension in renal hypertension is the diminished ability of the kidneys to excrete water and salt at any given level of arterial pressure. Addition of the angiotensin mechanism does not affect the level to which the arterial pressure rises but does reduce the cardiac output and blood volume, two effects that are different from those occurring in pure salt and water retention. It is exceedingly interesting that studies by Dustan and her associates (1970) on renal hypertension have shown exactly these same differences as follows: In those patients with renal hypertension who have a strong angiotensin component, both the cardiac output and the blood volume are decreased below normal. Conversely, those patients who have only the salt and water retention effects of renal hypertension but who have very low rates of angiotensin formation generally have normal or high cardiac outputs and blood volume.

COMMENT

This paper has had two principal goals: First, we have attempted to show how a total system of interrelated feedback mechanisms operate together to regulate arterial pressure, and especially to show how certain abnormalities of the system can lead to hypertension. Second, and perhaps even more important, we have hoped to demonstrate that many simple intuitive explanations for regulation of arterial pressure can often be markedly in error if one fails to consider the total system in a composite, analytical way. For instance, some of the basic intuitive concepts of the primary causes of different types of hypertension seem to be considerably in error when one studies the total picture of arterial pressure regulation in a systematic manner. At least, it is very clear that the analytical approach to understanding function of the bodily mechanisms can lead to far greater depths of meaning than can possibly be true when using the informal, intuitive approach.

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